What is the relationship between the intake of vegetable protein, including soy protein, and chronic disease?

Conclusion

Few studies are available and the limited body of evidence suggests that vegetable protein intake does not offer special protection against type 2 diabetes, coronary heart disease and selected cancers.

Grade: Limited

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here.

Evidence Summary Overview

This review included seven studies examining the relationship between vegetable protein or soy protein and coronary heart disease (CHD), type 2 diabetes mellitus (T2D), and cancer published since 2000. Six prospective cohort studies (Halton, 2006; Kelemen, 2005; Halton, 2008; Sluijs, 2010; Song, 2004; Lee, 2009) and one ecological study (Nagata, 2000) were reviewed. Five studies addressed vegetable protein and two studies focused on soy protein. Six of the studies reported on five large (N=37,000 to 85,000) unique prospective cohorts; three of the cohorts were from the US, one from the Netherlands and one from China. The two studies examining soy protein were both conducted outside of the US. Five of the seven studies included only women.

Coronary Heart Disease

- *Vegetable protein:* Two studies (Halton, 2006; Kelemen, 2005) examined the relationship between vegetable protein and CHD. Both studies were prospective cohort studies with women in the US. In the Nurses' Health Study (Halton, 2006), vegetable protein was inversely associated with the risk of CHD in the age- and smoking-adjusted model, but no relationship was observed in multivariate analyses. Using data from the Iowa Women's Health Study, Kelemen et al. (2005) estimated a 30% decrease in CHD mortality from an isoenergetic substitution of vegetable protein for carbohydrate and of vegetable protein for animal protein.
- *Soy protein:* Nagata (2000) conducted an ecological study in Japan and found no relationship between soy protein and heart disease mortality.

Type 2 Diabetes

Vegetable protein: Three prospective cohort studies (Halton, 2008; Sluijs, 2010; Song, 2004) examined the relationship between vegetable protein and T2D. Two studies (Halton, 2008; Song, 2004) were conducted with women in the US, and the third study (Sluijs, 2010) reported on men and women from the Dutch EPIC-cohort in the Netherlands. In the Nurses' Health Study (Halton, 2008), vegetable protein was inversely associated with T2D in the age-adjusted model, but no relationship was observed in multivariate analyses. No relationship between vegetable protein intake and T2D was observed in the Women's Health Study (Song, 2004) or the Dutch cohort of the EPIC study (Sluijs, 2010).

Cancer

- *Vegetable protein:* Substituting vegetable protein for carbohydrate or vegetable protein for animal protein did not significantly affect risk for cancer in the Iowa Women's Health Study (Kelemen, 2005)
- *Soy protein:* In the Shanghai Women's Health Study (Lee, 2009), an inverse relationship between soy protein intake and premenopausal breast cancer was observed, but no association was observed for postmenopausal breast cancer. The median intake for the highest soy protein quintile was 16.02 g per day. Nagata (2000) conducted an ecological study in Japan and observed no association between soy protein intake and breast, prostate or lung cancer mortality. However, a positive association between soy protein intake and colorectal cancer mortality and an inverse association between soy protein intake and stomach cancer mortality were observed. The mean (SD) soy protein intake was 6.5 (0.8)g per day.

Evidence Summary Paragraphs

Halton et al, 2006 (positive quality) examined the association between a low-carbohydrate diet score and risk of CHD in 82,802 women (age 30 to 55 years) from the Nurses' Health Study cohort in the US. Secondary analyses examined the association between vegetable protein intake and CHD risk. Non-fatal myocardial infarction (MI) was self-reported with follow-up confirmation, and fatal coronary events were identified from state vital records and National Death Index or reported by next of kin or the US Postal Service. Diet was assessed using a semi-quantitative food frequency questionnaire (FFQ) in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 1,994 cases of CHD were identified. Vegetable protein was inversely associated with the risk of CHD in the age- and smoking-adjusted model (RR between extreme deciles = 0.80; 95% CI: 0.63, 1.00; P for trend = 0.009). However, this association became non-significant in multivariate analyses (RR between extreme deciles = 1.08; 95% CI: 0.82, 1.43; P=0.59). The authors concluded that vegetable protein intake was not significantly associated with the risk of CHD according to multivariate analyses.

Kelemen et al, 2005 (neutral quality) investigated the associations of different protein sources with chronic disease mortality in 29,017 postmenopausal women (age 55 to 69 years) in the Iowa Women's Health Study (US). Mortality was ascertained through linkage with the National Death Index. Diet over the previous year was assessed with a semi-quantitative FFQ at baseline. During 15 years of follow-up, 4,843 new cancers, 739 CHD deaths, 1,676 cancer deaths, and 3,978 total deaths were identified. Among women in the highest intake quintile, CHD mortality decreased by 30% from an isoenergetic substitution of vegetable protein for carbohydrate (multivariate RR=0.70; 95% CI: 0.49, 0.99; P=0.02) and of vegetable for animal protein (multivariate RR=0.70; 95% CI: 0.51, 0.98; P=0.02). Risk ratios for cancer and all-cause mortality were not significant (NS) in fully adjusted models. The authors concluded that dietary proteins from animal and vegetable food sources appear to be differentially associated with mortality from CHD, specifically an inverse association of vegetable protein and a positive association of animal protein, when substituted for carbohydrates in the diet.

Halton et al, 2008 (positive quality) prospectively examined the association between a low-carbohydrate diet score and the risk of T2D among females in the US. Additional analyses examined the relationship between macronutrient intake, including vegetable protein and T2D. Participants were 85,059 women (age 30 to 55 years, 98% white) from the Nurses' Health Study cohort. Type 2 diabetes was ascertained by self-report on biennial questionnaires. If a participant reported a diagnosis of diabetes, a supplementary questionnaire was mailed regarding symptoms, diagnostic testing and treatment to confirm the diagnosis. Diet over the previous year was assessed

by means of a semi-quantitative FFQ in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 4,670 cases of T2D were documented. Vegetable protein was inversely associated with the risk of CHD in the age-adjusted model (RR between extreme deciles = 0.90; 95% CI: 0.77, 1.04; P=0.001). However, this association became non-significant in multivariate analyses (RR between extreme deciles = 0.97; 95% CI: 0.81, 1.17; P=0.36). The authors concluded that vegetable protein intakes were not associated with risk of T2D in women.

Sluijs et al, 2010 (positive quality), a prospective cohort study, examined the association among dietary total, vegetable and animal protein intake and T2D incidence among 38,094 participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. Participants were from the Dutch EPIC cohort. Incident diabetes was self-reported on questionnaires and verified against medical records. Dietary protein intake was measured with a self-administered validated 178-item FFQ. During 10 years of follow-up, 918 incident cases of diabetes were documented. Vegetable protein intake was not related to diabetes (HR between extreme quartiles = 0.84; 95% CI: 0.70, 1.01; P=0.10). Adjustment for confounders did not materially change these results.

Song et al, 2004 (positive quality) prospectively assessed the associations between red meat consumption and incidence of T2D in US women. Additional analyses examined the relation between vegetable protein intake and T2D. Participants were 37,309 women (age 45 years or more) from the Women's Health Study. Type 2 diabetes was ascertained by self-report on annual questionnaires with confirmation in a subset of the sample. Dietary intake was assessed with a 131-item semi-quantitative FFQ at baseline (1993). Over an average of 8.8 years, 1,558 incident cases of T2D were identified. In the fully adjusted model, multivariate RR comparing extreme quintiles of vegetable protein intake was 0.91 (95% CI: 0.73, 1.14; P=0.83). No association between T2D and vegetable protein intake was observed.

Lee et al, 2009 (positive quality) investigated the association of soy food intake in adolescence and adulthood with breast cancer risk among 73,225 women from the Shanghai Women's Health Study (age 40 and 70 years). Breast cancer was ascertained by a combination of biennial surveys and linkage with the Shanghai Cancer Registry and Shanghai death certificate registry. Diet was assessed with a validated FFQ at baseline and again two to three years later. The FFQ covered "virtually all soy foods consumed in urban Shanghai" including soy milk, tofu, soy products other than tofu, dried soybeans, soybean sprouts and fresh soybeans. Dietary intake during adolescence (between the ages of 13 and 15 years) was estimated using a brief FFQ, including 19 raw food items or groups, and soy food items, including soy milk, tofu and other soy products, dry soybeans, and fresh legumes, including soy beans. Over a mean follow-up of 7.4 years, 594 incident cases of breast cancer were identified. Soy protein intake was inversely associated with the overall risk of breast cancer, although the trend tests were not statistically significant (multivariate RR between extreme quintiles = 0.89; 95% CI: 0.66, 1.15; P=0.158). Soy protein was inversely associated with the risk of pre-menopausal breast cancer (multivariate RR between extreme quintiles = 0.41; 95% CI: 0.25, 0.70; P<0.001). No significant association with soy protein consumption was found for post-menopausal breast cancer (RR for extreme quintiles = 1.22; 95% CI: 0.87, 1.71; P=0.504). Women in the highest tertile of soy protein intake in both adolescence and adulthood had the greatest decrease in relative risk for pre-menopausal breast cancer compared with women in the lowest tertile of soy protein intake at both of these time points (RR: 0.41; 95% CI: 0.22, 0.75). The authors concluded that this prospective cohort study provided evidence of a protective effect of soy food, including soy protein, intake against pre-menopausal breast cancer.

Nagata, 2000 (neutral quality) examined correlations between soy product intake and mortality rates from several types of cancer and heart disease in an ecological study of approximately 6,000 randomly selected households in Japan. Age-standardized mortality rates for heart disease and

stomach, colorectal, lung, breast and prostate cancer were obtained from the National Vital Statistics, 1995. Soy intake was obtained from the National Nutritional Survey Report between 1980 and 1985 by annual three-day diet records. Soy items included in the survey were miso, tofu, fried tofu and soybeans, and the rest of soy products such as soy milk and yuba; estimation of soy protein intake was based on the food table used in the survey. Among men, there was a significant inverse association between soy protein and stomach cancer mortality (R=-0.31; P<0.05) in the adjusted model. Among men and women, there was a significant positive association between soy protein and colorectal cancer mortality (R=0.36; P<0.05; R=0.51; P<0.01, respectively) in adjusted models. No significant associations for lung, breast or prostate cancer were observed in adjusted models. There was NS association between soy protein and heart disease mortality in adjusted models. Nagata reported a modest inverse relationship between soy protein intake and stomach cancer mortality as well as a modest positive relationship between the intake of soy protein and colorectal cancer mortality in this ecological study in Japan.

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Author, Year, Study Design, Class, Rating	Study Name	Location	Vegetable Protein Association (Pos, Neg, None)	Soy Protein Association (Pos, Neg, None)
Halton et al 2006 Study Design: Prospective Cohort Study Class: B Rating: [+]	Nurses' Health Study.	US.	Ø Coronary Heart Disease (CHD).	Not examined.
Halton TL, Liu S et al, 2008 Study Design: Prospective cohort Class: B Rating: [+]	Nurses' Health Study.	US.	Ø Type 2 Diabetes (T2D).	Not examined.
Kelemen et al 2005 Study Design: Prospective cohort study	Iowa Women's Health Study.	US.	*Substituting veg. protein for CHO:* (-) CHD mortality Ø Cancer	Not examined.

Class: B Rating:			Ø All-cause mortality *Substituting veg. protein for animal protein:* (-) CHD mortality Ø Cancer Ø All-cause mortality.	
Lee et al 2009 Study Design: Prospective Cohort Study Class: B Rating:	Shanghai Women's Health Study.	China.	Not examined.	(-) Pre-menopausal breast cancer Ø Post-menopausal breast cancer.
Nagata 2000 Study Design: Longitudinal study Class: C Rating:	Ecological study.	Japan.	Not examined.	Ø Heart disease mortality Ø Breast, prostate cancer mortality (+) Colorectal cancer mortality.
Sluijs I, Beulens JW et al, 2010 Study Design: Prospective cohort study Class: B Rating:	European Prospective Investigation into Cancer and Nutrition (EPIC)-NL.	The Netherlands.	Ø T2D.	Not examined.

Song Y, Manson JE et al, 2004 Study Design: Prospective cohort study Class: B Rating: ⊕	Women's Health Study.	US.	Ø T2D.	Not examined.

Research Design and Implementation Rating Summary

For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

📄 Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9;355(19):1991-2002.

📄 Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008; 87 (2): 339-346.

📄 Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol.* 2005;161(3):239-249.

📄 Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am J Clin Nutr. 2009 Jun;89(6):1920-6.

📄 Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol.* 2000 Oct;29(5):832-6.

📄 Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33 (1): 43-48. Epub 2009 Oct 13.

📄 Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the Women's Health Study. *Diabetes Care.* 2004; 27(9): 2,108-2,115.